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Long QT syndrome, cardiovascular anomaly and findings in ECG-guided genetic testing☆

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ABSTRACT

Objective: Patients with inherited long QT syndrome (LQTS) are prone to torsade de pointes and sudden death (SD). Identifying affected individuals is important for SD prevention. This study aimed to determine the cause and genotype–phenotype characteristics of LQTS in a large Omani family.
Methods: Upon LQTS diagnosis of a 5-year-old girl (proband), targeted mutation screening was performed based on the gene-specific ECG pattern identified in her mother. ECG-guided family genotyping was conducted for identifying additional affected individuals.
Results: ECGs of the proband demonstrated 2:1 AV block, incomplete right bundle branch block (IRBBB) and markedly prolonged QTc (571–638 ms) with bizarre T waves. Cardiac imaging revealed dilatation of the ascending aorta and pulmonary artery, and left ventricular non-compaction. Her parents were first cousins. Both showed mild QT prolongation, with the mother presenting a LQT2 T wave pattern and the father IRBBB. Targeted *KCNH2* screening identified a novel homozygous frameshift mutation p.T1019Pfs × 38 in the proband within 3 days. Family genotyping uncovered 3 concealed LQT2 and confirmed 11 members showing LQT2 ECG patterns as heterozygous mutation carriers. All heterozygous carriers were asymptomatic, with 71% showing normal to borderline prolonged QTc (458 ± 33 ms, range 409–522 ms).
Conclusion: p.T1019Pfs × 38, a novel *KCNH2* mutation, has been identified in a large LQTS family in Oman. Consanguineous marriages resulted in a homozygous with severe LQTS. ECG-guided phenotyping and genotyping achieved a high efficiency. Genetic testing is essential in identifying concealed LQTS. Further investigation is warranted to determine if there is a causative relationship between homozygous p.T1019Pfs × 38 and cardiovascular anomaly.

1. Introduction

Long QT syndrome (LQTS), a cardiac ion channelopathy, is characterized by a prolonged QT interval on body surface electrocardiogram (ECG) associated with increased susceptibility to torsade de pointes (TdP) and sudden death (SD) under certain circumstances [1–4]. TdP is an atypical type of polymorphic ventricular tachycardia (VT) mostly seen in the presence of a markedly prolonged QT interval [3,5,6]. LQTS can be classified as acquired and inherited though genetic predisposition also plays a role in some of the acquired forms [7]. In general, acquired LQTS can be resolved by removing the causes, whereas inherited LQTS is permanent due to mutations of genes encoding or regulating cardiac potassium, sodium and calcium ion channels [8–10]. To date, over 1000 mutations in more than 15 genes have

Abbreviations: NMD, nonsense-mediated mRNA decay.

☆ Khalfan S. AlSenaidi and Guoliang Wang have equally contributed to this study as co-first authors for conducting family phenotyping and genotyping respectively. Li Zhang has designed and organized the study; Yuxin Fan is responsible for the genetic aspects in the study. Dominik A. Beer created the family pedigree. All authors have contributed significantly in delivering the study, data analysis and manuscript development. Other than Li Zhang who is supported by W.W. Smith Charitable Trust, all have no conflict of interest to disclose and agreed with what is written.

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been reported to cause LQTS with the vast majority as LQT1-3 [11–13]. Gene-specific ECG patterns, reflecting the altered electrophysiological properties of cardiac repolarization due to mutant ion channel genes [14], are present in the majority of LQT1-3 mutation carriers [15], Other than the delayed ventricular repolarization and rhythm disturbance during cardiac events, LQTS itself does not affect cardiac mechanical function at the non-event state. In other words, LQTS hearts are otherwise healthy, which may be the reason TdP can revert to sinus rhythm spontaneously in most cases. Nevertheless, even in a healthy heart there is a 5% probability that TdP will degenerate into ventricular fibrillation, leading to SD [16]. Thus identifying affected individuals is essential for SD prevention.

Currently genetic testing of known LQTS-causing genes is commercially available. Once a LQTS-causing mutation is identified in one family member, screening blood relatives can reveal additional affected members. Family screening is a major resource for finding affected individuals with LQTS [2,17] that will not only allow affected members to take actions necessary for SD prevention but also provide relief to non-mutation carriers. Despite these benefits, commercial genetic screening is largely not an option for families in developing countries due to the high cost of screening for >15 known genes. However, LQTS is a single gene disorder in most cases and the ECG phenotype is very characteristic in LQT1-3, the most common genotypes. Performing targeted mutational screening based on gene-specific ECG patterns identified in one or more family member(s) can be utilized for family genotyping. The aim of this study is to demonstrate the effectiveness of ECG-guided phenotyping and genotyping in identifying homozygous and heterozygous carriers of a novel *KCNH2* mutation in a large family in the Sultanate of Oman.

2. Methods

2.1. Study subjects

The proband, a 5-year-old girl, and her family members were enrolled in the study after informed written consent was obtained from study subjects or their legal guardians.

2.2. ECG-guided phenotyping

ECGs of the proband and her parents were evaluated to determine if gene-specific ECG patterns were present. Subsequently, an ECG pattern guided family phenotyping [17] was conducted based on the screening strategy demonstrated in Fig. 1.

A standard 12-lead ECG (0.05 Hz–100 Hz, 25 mm/s for the paper speed and 10 mm/mV for the voltage) was recorded in the supine resting state in all subjects. At the time the ECG was obtained, none of the participants were taking beta-blockers or QT-prolonging drugs. ECGs were analyzed by two investigators (K.S.A.S and L.Z.) for heart rate, rhythm, QT interval and the presence/absence of gene-specific ECG patterns.

The QT interval was measured manually in the lead showing the longest QT interval. The termination of the T wave was taken to be the point of maximal change in the slope as the T wave merges with the base line [2]. QT and R–R cycle length were averaged from 3 to 5 consecutive beats. In the presence of sinus arrhythmia, average R–R cycle length was obtained from consecutive beats in 10 s or from the heart rate. The U wave was excluded from QT measurement. Since all ECGs were taken in the resting state, QT was corrected (QTc) by using Bazett's formula [18].

Family phenotyping was carried out prior to genetic testing. By following the screening strategy shown in Fig. 1, Individuals were considered phenotypically affected if they presented with both LQT2 T wave patterns and diagnostic QTc (≥470 ms in males or ≥480 ms in females), and possibly affected if a LQT2 T wave pattern was present in the absence of a diagnostic QTc [2,17].

History included LQTS-related syncope, cardiac arrest, sudden death, and consanguineous marriage if present. A family pedigree was first established for the proband and her parents. It was then expanded by following the gene-specific ECG pattern identified in blood relatives in each generation.

Since the proband was found to have structural heart abnormalities at birth, she had a regular follow-up every 4–6 months. Her antenatal, past medical history and medical records including ECG, 24-hour Holter, 2D-echocardiography and cardiac computed tomography (CT) were reviewed. Echocardiogram was also obtained from her parents to determine whether they had structural cardiovascular abnormalities.

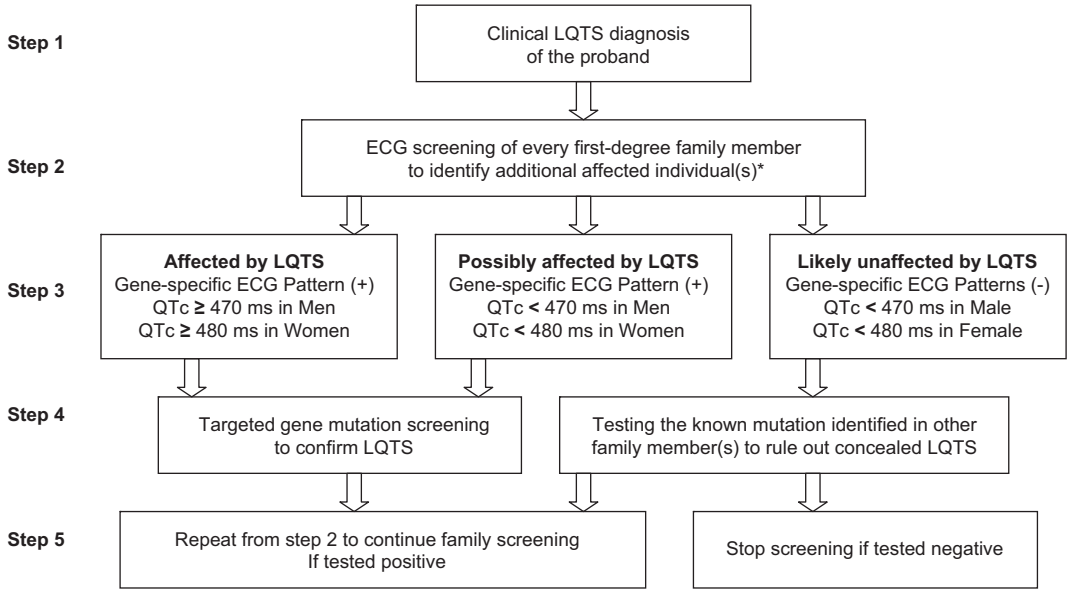

Fig. 1. This flow chart demonstrates the strategy of ECG-guided family phenotyping and genotyping in a LQTS family if a gene-specific ECG pattern is present.

2.3. ECG-guided genotyping

Informed consent, approved by and in accordance with the guidelines of the Institutional Review Board of Baylor College of Medicine, was obtained from every study subjects prior to genetic testing. Based on the gene-specific T wave pattern shown in the mother of the proband, we took the approach of targeted gene mutation screening.

DNA isolation, PCR and sequence analysis were performed according to the standard protocol [11]. Briefly, genomic DNA was extracted from peripheral blood leukocytes using QIAamp DNA blood midikit (QIAGEN). Primer pairs were designed to amplify all of the coding regions and the intron–exon boundaries of *KCNH2* based on the published sequence (GenBank accession number NM_000238.3). PCR amplifications were performed using standard protocols, and PCR products were analyzed by direct sequencing on an Applied Biosystems 3730XL Genetic Analyzer with BigDye Terminator chemistry (version 3.1). The procedure was repeated upon identification of mutation(s) in order to rule out sequencing artifacts.

2.4. Statistical analysis

NCSS 2007 (Kaysville, Utah), a software for biomedical statistics, was used for data analysis. Continuous data were expressed as mean ± SD while categorical data were presented as counts (%). Heart rate, QRS duration, QTc and presence of gene-specific T wave patterns were compared between affected individuals and non-affected family members using two-sample t tests for normally distributed variables. Chi-square test was used for comparisons of categorical variables. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Phenotyping

3.1.1. Proband

The proband is a 5-year-old Omani girl with a history of fetal tachyarrhythmia and non-immune hydrops fetalis (scalp edema and ascites) for which the mother was started on digoxin. She was born at term with a birth weight of 2.4 kg. Soon after birth she was found to have bradycardia with a heart rate in the range of low 60's/bpm, intermittent 2:1 AV block and paroxysmal VT. She was treated with amiodarone and propranolol. Her initial echocardiogram after birth showed mild left ventricular hypertrophy and a dilated ascending aorta (AscAo, 16 mm). Her cardiac systolic function was normal. Multiple 24-hour Holter recordings showed VT runs lasting from a few seconds to a minute. After one month of age, no VTs were noted on her Holter recordings but she continued to have bradycardia. Amiodarone was weaned off at the age of 6 months and the family then elected to stop propranolol at the age of 1.5 year. At age 3.5 years, she developed her first syncopal episode one day after fever, vomiting, diarrhea, and acetaminophen intake. At the local Accidental & Emergency Service, recurrent TdP was revealed. She was treated and became hemodynamically stable. Serial ECGs from age 3.5 to 5 years showed sinus bradycardia, increased QRS amplitude in both right and left precordial leads, intermittent 2:1 AV block, incomplete right bundle branch block (IRBBB), and a markedly prolonged QT interval (QTc 612 ± 26 ms, range 571–638 ms) with bizarre and inverted T waves in most of the 12 leads. (Fig. 2a)

A recent echocardiogram at the age of 5 years showed the following changes: AscAo 24 mm with a Z score of 4.5 (Fig. 3-a). Echocardiogram also revealed that her left ventricular apex had increased trabeculations and deep recesses that met the diagnostic criteria for left ventricular non-compaction (LVNC, Fig. 3-b). In addition, she had a normal aortic root size of 18.6 mm (Z score 0.21), sinotubular junction 17.8 mm (Z score 1.4), and aortic annulus 13.2 mm (Z score 0.23) with no aortic regurgitation. This child also had a dilated main pulmonary artery (MPA) and branch pulmonary arteries which were confirmed by cardiac CT (Fig. 3-c). She had a normal pulmonary artery pressure with normal right ventricular size and normal biventricular systolic function (EF 68%). Otherwise, she has been developing normally and event-free with no clinical evidence of Marfan syndrome or Loeys–Dietz syndrome.

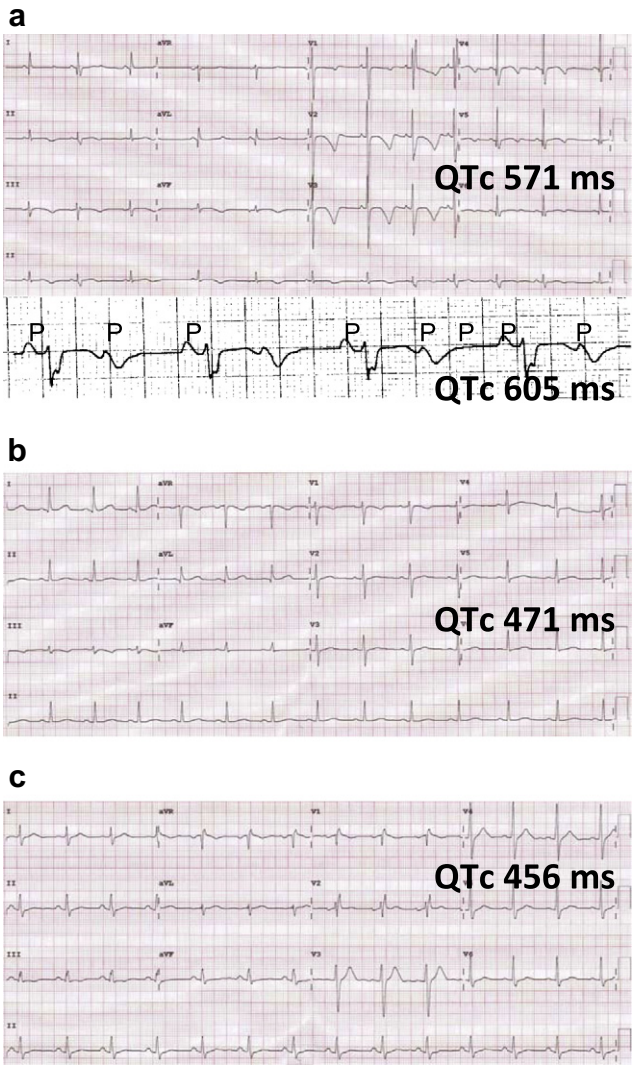

Fig. 2. ECG characteristics in the proband and her parents. a. The top panel shows a 12-lead ECG of the proband. A rate-dependent IRBBB is noted. T waves are inverted in leads II, III, aVF and V1-4. ECG tracing (Lead II) in the bottom panel demonstrates functional 2:1 AV block. Marked QT prolongation is shown in both ECG tracings. b. A typical LQT2 T wave morphology is shown in the mother c. The father's ECG shows IRBBB and a borderline QT interval. His T wave morphology is atypical for LQT2.

She has normal hearing. She is continuing on propranolol with the dose adjusted for her weight. No VTs have been detected on repeat Holters after having re-started propranolol.

3.1.2. Parents and the extended family members

Parents of the proband are first cousins. Both have been asymptomatic. Family history revealed that the proband's maternal grandmother was having uncontrolled seizures. Despite medical therapy she died suddenly in her 30s. Unfortunately no medical records could be obtained. ECGs of the mother showed prolonged QTc (471–499 ms) with subtle bifid T waves in most of 12-leads, an ECG pattern typically seen in LQT2 [15,17,19]. The proband's father had an IRBBB, borderline QTc (456–463 ms) with an atypical T wave morphology. Unlike their daughter, they had no structural cardiovascular abnormalities. The maternal and paternal grandfathers were brothers. Both presented with a typical LQT2 phenotype manifest, a prolonged QT interval with LQT2 T wave

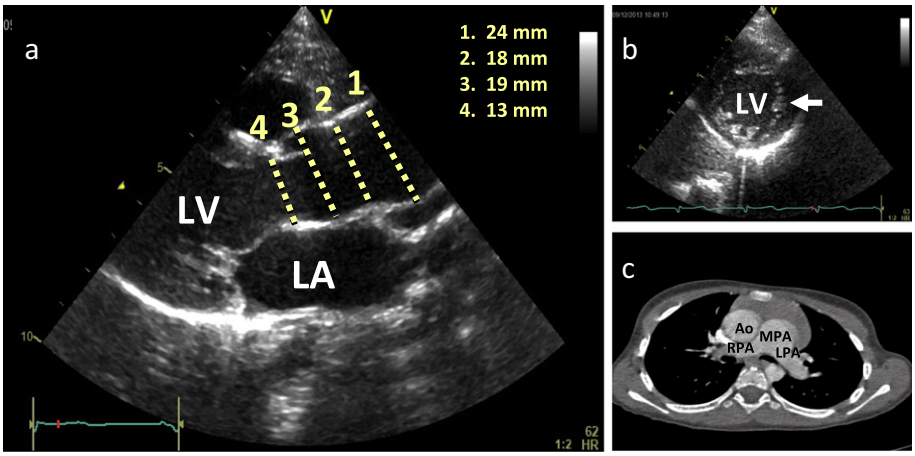

Fig. 3. Echocardiogram and cardiac CT images of the proband. a. High parasternal echocardiographic long axis view showing the diameters of the proximal aorta with clearly dilated ascending aorta. LA: left atrium, LV: left ventricle. b. Echocardiographic short axis view of the left ventricular apex showing the prominent trabeculations and deep recesses of the non-compacted endocardial layer (arrow). c. Computed tomography scan of the chest (axial view) showing the dilated ascending aorta (Ao), main pulmonary artery (MPA), left and right pulmonary arteries (LPA and RPA).

patterns. ECG screening of the great grandfather revealed a LQT2 phenotype. ECG screening each of their offspring revealed seven children with LQT2 phenotype. Overall, among 1st, 2nd and 3rd degree blood relatives showing typical LQT2 T wave patterns, 3/11 presented with normal QTc (407–440 ms), 5/11 with borderline QTc (455–465 ms) and the remaining with moderate to markedly prolonged QTc (470–522 ms).

3.2. Genetic testing and genotype–phenotype correlation

c.3504delC (p.T1019Pfs × 38), a novel homozygous frameshift mutation (Fig. 4), was identified in the proband within 3 days after targeted *KCNH2* gene screening based on the LQT2 ECG phenotype shown in her mother.

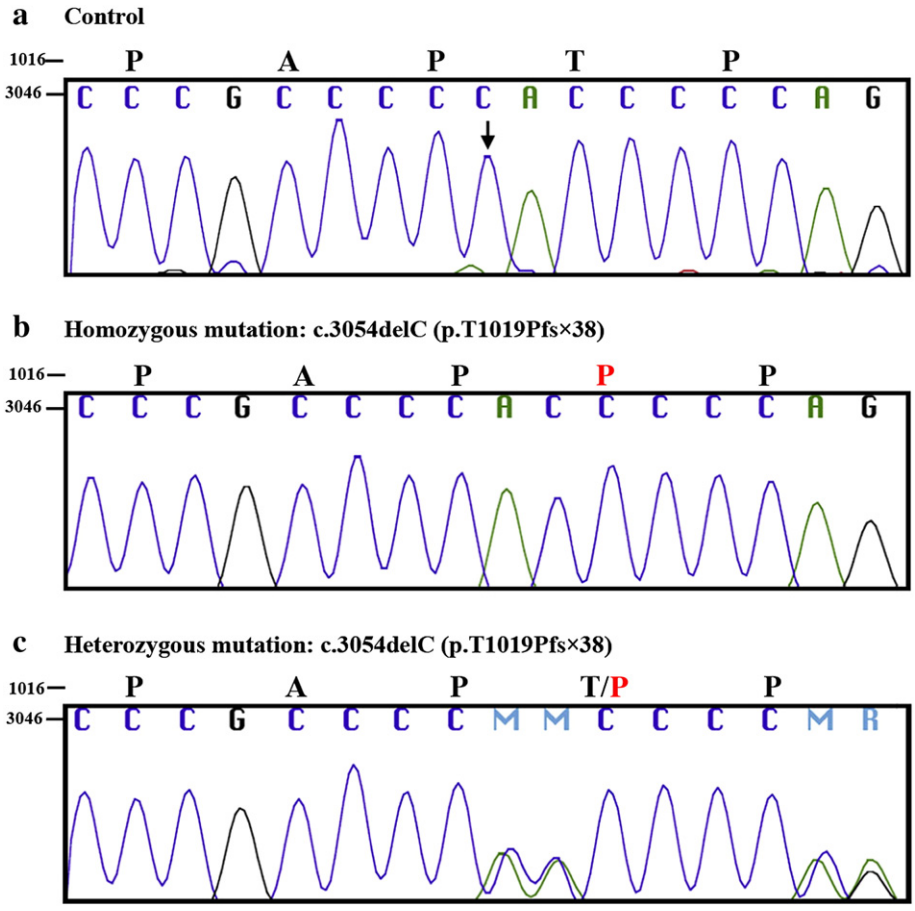

Fig. 4. The novel frameshift mutation. Sequencing analysis of *KCNH2* gene in the index patient (proband) and her family members shows a single nucleotide deletion at position 3504 (c.3504delC) which causes a frameshift mutation (p.T1019Pfs × 38). Panel A represents the normal control sequence of *KCNH2* (GenBank accession number NM_000238.3) with the amino acids at the top. Panel B demonstrates the homozygous deletion and the corresponding change of amino acids in the proband. Panel C shows the heterozygous deletion and the corresponding change of amino acids in her family members. The black arrow indicates the deleted nucleotide in Panels B and C.

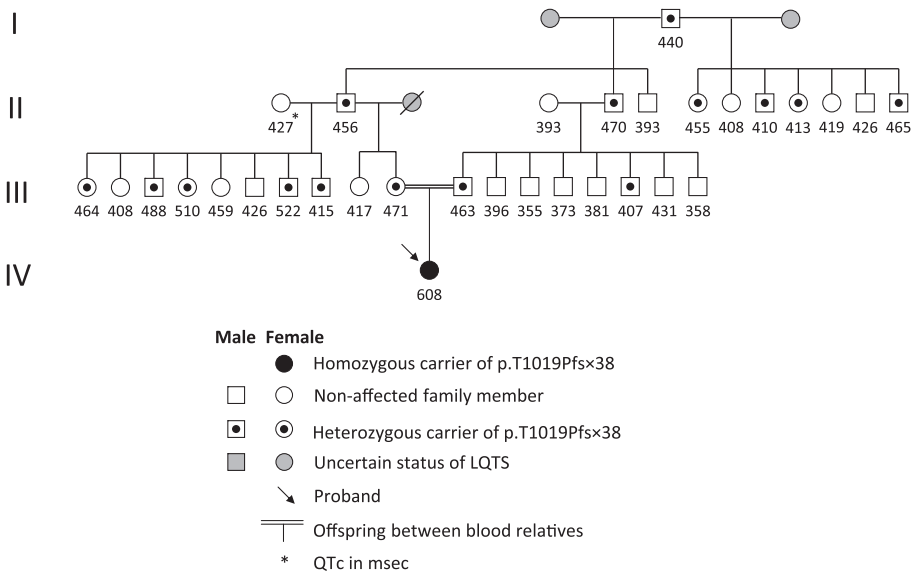

Fig. 5. Family pedigree. Pedigree structure demonstrates the penetrance of LQT2 through generations; and a homozygous mutation carrier (the proband) resulting from a consanguineous marriage. The pedigree is modified to protect patient and family privacy.

ECG-guided genotyping of the family encompassing four generations identified a total of 15 mutation carriers, including one homozygous (proband) and 14 heterozygous carriers (Fig. 5). Table 1 shows the phenotype characteristics of all mutation carriers with comparisons to non-affected family members. This mutation has never before been reported.

4. Discussion

In this study, we identified c.3504delC (p.T1019Pfs × 38a), a novel frameshift mutation in *KCNH2* gene, in 15/35 (42%) of family members in a 4-generation Omani family. The proband is a homozygous mutation carrier presenting with a severe LQTS phenotype, whereas 11/14 heterozygous mutation carriers presented with a typical LQT2 ECG phenotype, suggesting c.3504delC (p.T1019Pfs × 38a) closely co-segregated with LQTS.

In the C-terminal region, c.3504delC is located in exon 13 of *KCNH2*, causing p.T1019Pfs × 38a a frameshift reading error at the protein level. Based on the functional expression results revealed in Q1070X, a nonsense mutation 51 base-pair away, c.3504delC (p.T1019Pfs × 38) is predicted to be a functional mutation especially when the co-segregated genotype–phenotype is considered [19,20].

In general, nonsense and frameshift mutations can cause premature stop codons (PTCs) in the transcribed mRNA, resulting in truncated, incomplete, and usually nonfunctional protein products. Over 30% of LQT2-causing mutations are nonsense and frameshift mutations that can introduce PTCs. Nevertheless, an evolutionary surveillance called nonsense-mediated mRNA decay (NMD) pathway can detect and selectively degrade defective mRNA transcripts containing PTCs, thereby preventing the synthesis of truncated and potentially harmful proteins [19–21]. As such, dominant-negative effects from truncated proteins can be converted to haploin sufficiency. In fact, heterozygous Q1070X carriers of an Arabian family reported by Bihuiyan, et al. [20] and heterozygous p.T1019Pfs × 38a carriers of an Omani family in our study, all presented with mild LQT2 phenotypes. It is interesting to note that the IRBBB is shown in both the father and daughter, indicating that such an ECG pattern can be inherited as well since the prevalence of IRBBB is only 2% in the general population.

Oman is an Arab state on the southeastern coast of the Arabian Peninsula. Consanguineous marriage is a marriage between blood relatives. Consanguineous marriage is practiced in most Arab and Middle Eastern countries, including Oman. More than half (52%) of marriages are consanguineous. First cousin marriages are the most common, constituting 39% of all marriages and 75% of all consanguineous marriages in Oman [22]. The parents of the proband are first cousins and both are heterozygous carriers of T1019Pfs × 38a mutation. The chance that each of their offspring becomes a heterozygous, a homozygous or a non-mutation carrier is 50%, 25% and 25%, respectively (Fig. 6). Such a pattern of autosomal dominant inheritance, in the setting of both parents being heterozygous, is actually the same as autosomal recessive inheritance. Due to the nature of consanguinity, it is anticipated that additional genetic defects, especially autosomal recessive disorders,

Table 1
Phenotype characteristics in p.T1019Pfs × 38 mutation carriers and non-carriers.

	Homozygous mutation carrier[a]	Heterozygous mutation carriers	Non-mutation carriers
Age, yrs; mean ± SD (range)	5	26 ± 21 (4–82)	23 ± 13 (0.9–54)
Male/female, (%)	0/1	10/4	10/10
Heart rate, bpm;	79 ± 12	78 ± 15	76 ± 15
QRS duration, ms;	99 ± 16	85 ± 12	84 ± 11
Functional 2:1 AV block	Yes	No	No
QTc, ms; mean ± SD (range)	612 ± 26 (571–638)	458 ± 33 (407–522)[b]	409 ± 28 (355–459)
T wave pattern typical to LQT2, No (%)	No	11/14 (79%)[b]	0/20 (0)
LQTS-related symptoms	Syncope	No	No

[a] ECG values of the proband were obtained from serial ECGs.
[b] $p < 0.001$ when compared with non-mutation carriers in the family.

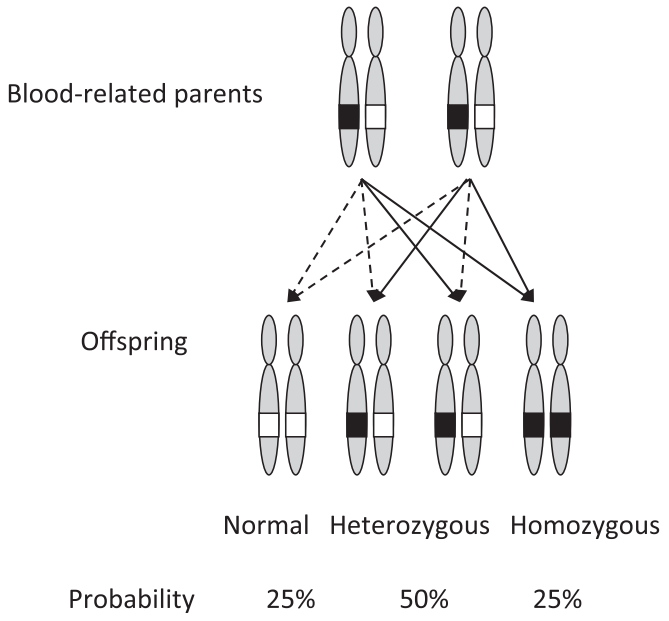

Fig. 6. Pattern of inheritance.

may be present in the family. For example, the father of the proband has seven siblings. Two of them suffer from congenital deafness even though they do not carry this KCNH2 mutation. Congenital deafness is fairly common in Omani families with consanguineous marriages [23].

The proband carries two doses of T1019Pfs × 38a mutation. As predicted, the NMD effects [19–21] may have led to a nearly complete elimination of hERG channels, therefore producing a severe LQTS phenotype [19,20,24]. The severe clinical phenotype observed in the proband is consistent with a simulation study in a cardiac ventricular cell model [25]. The computer simulation study shows that a 75–100% reduction of hERG channel currents can prolong action potential duration sufficiently to generate early after depolarizations, which may trigger life-threatening arrhythmias. Indeed the proband had an early onset of cardiac events due to recurrent TdP. Her ECG displayed an extremely prolonged QT interval, which at times, caused functional 2:1 AV block because every other P wave of sinus node origin appeared on the ascending portion of the T wave of the previous beat (Fig. 2a) when the AV conduction system was absolutely refractory. In LQTS, functional 2:1 AV block is reported in children with LQT3 [26,27], LQT8 (Timothy syndrome) [28] or compound mutations of LQTS [29] with a severe phenotype.

The ECG of the proband displayed a bizarre and inverted T wave in most of the 12 leads, which is atypical for LQT2. Indeed most of LQT2 patients present with gene-specific T wave patterns except those carrying compound mutations. To our knowledge, the proband is the first case of LQTS associated with dilatation of the ascending aorta and pulmonary arteries, and the development of LVNC. Those changes are different from Marfan syndrome, Loeys–Dietz syndrome, or other readily explainable syndromes. Neither parents of the proband nor other family members had such changes. To date, LVNC has been reported in several patients showing severe LQTS phenotype and they happen to be the mutation carriers of *KCNQ1* [30], *KCNH2* [31] and *SCN5A* [32]. The proband in our study is the 3rd case of LVNC carrying a *KCNH2* mutation. Whether it is caused by homozygous p.T1019Pfs × 38 or other genetic defects will require further investigations, which is beyond the scope of current study.

Based on our experience, most LQTS cases are identified via family screening [17,19,33]. Since LQT2 is one of the most common subtypes of LQTS with gene-specific ECG pattern shown in the majority of gene carriers, once a LQT2 ECG pattern is identified in a LQTS subject, performing ECG-guided family screening has been proven to be a highly effective approach not only in improving the diagnostic accuracy but also in finding the gene mutation. In this study we bypassed 15 LQTS gene screening tests [13] that otherwise could cost a fortune to the family. A targeted *KCNH2* gene screening only took 3 days to identify the mutation with minimal cost. ECG-guided family phenotyping revealed family branches to which the disease had penetrated. Genotyping everyone in a branch where one or more members express a LQT2 phenotype can also identify concealed cases. A total of 15 LQTS patients, 80% children and young adults, have been identified via ECG-guided phenotyping and genotyping. This cost-effective approach is especially suitable to patients and families in developing countries since the gene-specific ECG patterns can easily be recognized. Knowledge of genotype will help the affected individuals avoid QT prolonging drugs and metabolic factors that could predispose to TdP.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgment

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